5-FLUOROURACIL PLUS THYMIDINE OR LEUCOVORIN BY CONTINUOUS I.V. INFUSION
IN THE TREATMENT OF ADVANCED COLORECTAL CARCINOMA

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INTRODUCTION

5-Fluorouracil (FUra) has been the drug of choice in the treatment of colorectal cancers (1,2), and it is widely utilized in a variety of other malignancies (3). FUra exerts its antiproliferative effect following metabolic activation to various nucleotides (Chart 1). 5-Fluorouridine triphosphate (FUTP), due to its resemblance with uridine triphosphate (UTP), is incorporated into RNA (4-7); the consequence of this incorporation is the production of fraudulent mRNA, rRNA and tRNA which can ultimately cause cell death. The other proposed mechanism for FUra cytotoxicity is the inhibition of thymidylate synthetase (dTMP-S) by 5-fluorodeoxyuridine monophosphate (FdUMP) (8-11), leading to decreased thymidine triphosphate (dTTP) pools and to inhibition of DNA synthesis. The biochemical mechanism by which FdUMP binds to dTMP-S involves a cofactor, \(N^5,10\text{CH}_2\text{FH}_4\). Santi et al. have calculated that the dissociation constant (Kd) of the ternary complex FdUMP-dTMP-S\(N^5,10\text{CH}_2\text{FH}_4\) is of the order of \(5x10^{-11}\text{M}\). In absence of the reduced folate cofactor, FdUMP binding to dTMP-S is relatively weak, with a Kd of about \(10^{-5}\text{M}\) (9). An additional proposed mechanism of cytotoxicity of FUra is its incorporation into DNA (12-15). To date, little is known about the biological significance of this finding.
Pharmacological (narrow therapeutic index, short elimination half-life) and cytokinetic (phase-specificity) rationales were proposed to suggest the need for an evaluation of this agent by continuous i.v. infusion. However, clinical trials over the last fifteen years have demonstrated that different FUra regimens of i.v. administration, although appearing to affect the spectrum and degree of host toxicity (Table 1), do not seem to alter the therapeutic efficacy of this agent to any significant extent. In fact, despite the variety of the schedules employed, the response rate of colorectal cancer patients to this agent is still about 20% (1,3).

One approach to increase the selectivity of antimetabolites has been the administration of per se non-cytotoxic substances which can 'force' the metabolism of a drug in a selective way, resulting in an improved therapeutic index (16). An appropriated modulation with metabolites or cofactors could either increase the sensitivity of tumor cells or reduce the sensitivity of normal cells to a given anticancer drug, resulting in a favourable net effect. The clinical use of high-dose methotrexate with leucovorin rescue is a practical example of such useful modulations.